

being developed as therapeutic agents. Accordingly, there exists a need for compositions and methods for use in identifying biomarkers of IFN γ production in IFN γ -related disorders.

Summary

[0004] The compositions and methods provided herein use a fully human IgG1 anti-interferon gamma (IFN γ) monoclonal antibody (mAb) referred to herein as NI-0501, which binds and neutralizes IFN γ . NI-0501 binds to soluble and receptor (IFN γ R1)-bound forms of IFN γ . The compositions and methods provided herein are useful in the treatment of hemophagocytic lymphohistiocytosis (HLH).

[0005] The anti-IFN γ antibody referred to herein as NI-051 comprises a variable heavy chain complementarity determining region 1 (VH CDR1) comprising the amino acid sequence of SYAMS (SEQ ID NO: 1); a variable heavy chain complementarity determining region 2 (VH CDR2) comprising the amino acid sequence of AISGSGGSTYYADSVKG (SEQ ID NO: 2); and a variable heavy chain complementarity determining region 3 (VH CDR3) comprising the amino acid sequence of DGSSGWYVPHWFDP (SEQ ID NO: 3); a variable light chain complementarity determining region 1 (VL CDR1) comprising the amino acid sequence of TRSSGSIASNYVQ (SEQ ID NO: 4); a variable light chain complementarity determining region 2 (VL CDR2) region comprising the amino acid sequence of EDNQRPS (SEQ ID NO: 5); and a variable light chain complementarity determining region 3 (VL CDR3) region comprising the amino acid sequence of QSYDGSNRWM (SEQ ID NO: 6). The NI-0501 comprises the heavy chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 47, and the light chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 48.

[0006] In the compositions and methods provided herein, NI-0501 is formulated as a sterile concentrate for infusion (per mL). In some examples, NI-0501 is formulated as follows: 5 mg of NI-051, 1.55 mg L-histidine, 3.14 mg L-histidine monohydrochloride, monohydrate, 7.31 mg sodium chloride (NaCl), and 0.05 mg Polysorbate 80, where the pH is between 5.8 and 6.2. In some examples, NI-0501 is formulated as follows: 5 mg of NI-051, 1.55 mg L-histidine, 3.14 mg L-histidine monohydrochloride, monohydrate, 7.31 mg sodium chloride (NaCl), and 0.05 mg Polysorbate 80, where the pH is 6.0.

[0007] In the compositions and methods provided herein, NI-0501 is administered to a subject in need thereof for treating, preventing and/or delaying the onset or progression of, or alleviating a symptom associated with HLH. In some examples, NI-0501 is

administered to a subject in need thereof by IV infusion over a period of one hour at an initial dose of 1 mg/kg. In certain patient populations, e.g., those with low body weight and/or the very young, the IV infusion may last more than one hour, for example, at least 90 minutes, at least 2 hours, or at least 3 hours or greater.

[0007a] In one aspect, the present disclosure refers to use of an anti-interferon gamma (IFN γ) antagonist in the manufacture of a medicament for alleviating a symptom of a disorder, wherein a level of CXCL9 is detected, alone or in conjunction with one or more other biomarkers in a biological sample from a subject, the detected level of CXCL9 is compared to a control level of expression, and when the detected level is elevated, the medicament is to be administered in an amount sufficient to alleviate the symptom of the disorder to the subject.

[0007b] In another aspect, the present disclosure refers to use of an anti-interferon gamma (IFN γ) antagonist in the manufacture of a medicament for preventing graft failure in a patient who has received or will receive an allogeneic hematopoietic stem cell transplant.

[0008] In some examples, NI-0501 is administered to a subject in need thereof by at least one additional IV infusion after the initial IV infusion over a period of one hour at an initial dose of 1 mg/kg. In some examples, the at least one additional IV infusion is at a dose that is higher than the initial dose of 1 mg/kg. In some examples, the at least one additional IV infusion dosage is 3 mg/kg. In some examples, the at least one additional IV infusion is administered at least three days after the initial IV infusion. In some examples, the at least one additional IV infusion is administered at a time selected from the group consisting of at 3 days after the initial IV infusion, at 6 days after the initial IV infusion, at 9 days after the initial IV infusion, at 12 days after the initial infusion, and at 15 days after the initial infusion. In some examples, the at least one additional IV infusion is administered at 3 days after the initial IV infusion, at 6 days after the initial IV infusion, at 9 days after the initial IV infusion, at 12 days after the initial infusion, and at 15 days after the initial infusion.

[0009] In some examples, NI-0501 is administered to a subject in need thereof by at least one series additional IV infusions after the initial IV infusion over a period of one hour at an initial dose of 1 mg/kg, where the series of additional IV infusions includes at least one series of twice weekly IV infusions. In some examples, the at least one series of twice weekly IV infusions is administered at a dose higher than the initial dose of 1 mg/kg. In some examples, the at least one series of twice weekly IV infusions is administered at a dose of 3 mg/kg. In some examples, the at least one additional IV infusion is administered at least three weeks after the initial IV infusion. In some examples, the at least one additional IV infusion is administered at a time selected from the group consisting of at 3 weeks after the initial IV infusion, at 4 weeks after the initial IV infusion, at 5 weeks after the initial IV infusion, at 6 weeks after the initial infusion, at 7 weeks after the initial infusion, and at 8 weeks after the initial infusion. In some examples, the at least one additional IV infusion is administered at 3 weeks after the initial IV infusion, at 4 weeks after the initial IV infusion, at 5 weeks after the initial IV infusion, at 6 weeks after the initial infusion, at 7 weeks after the initial infusion, and at 8 weeks after the initial infusion.

[0010] In some examples, NI-0501 is administered to a subject in need thereof by at least two additional IV infusions after the initial IV infusion. In some examples, the at least two additional IV infusions are at a dose that is higher than the initial dose of 1 mg/kg. In some examples, the first additional IV infusion and the second additional IV infusion are administered at the same dosage. In some examples, the first additional IV infusion and the second additional IV infusion are administered at the same dosage that is higher than the initial dose. In some examples, at least one of the first and second additional IV infusions is administered at a dosage of 3mg/kg. In some examples, the first additional IV infusion is administered at least three days after the initial IV infusion. In some examples, the first additional IV infusion is administered at a time selected from the group consisting of at 3 days after the initial IV infusion, at 6 days after the initial IV infusion, at 9 days after the initial IV infusion, at 12 days after the initial infusion, and at 15 days after the initial infusion. In some examples, the first additional IV infusion is administered at 3 days after the initial IV infusion, at 6 days after the initial IV infusion, at 9 days after the initial IV infusion, at 12 days after the initial infusion, and at 15 days after the initial infusion. In some examples, the second additional IV infusion is administered at a time selected from the group consisting of at 3 weeks after the initial IV infusion, at 4 weeks after the initial IV infusion, at 5 weeks after the initial IV infusion, at 6 weeks after the initial infusion, at 7 weeks after the initial infusion, and at 8 weeks after the initial infusion. In some examples, the second additional IV infusion is administered at 3 weeks after the initial IV infusion, at 4 weeks after the initial IV infusion, at 5 weeks after the initial IV infusion, at 6 weeks after the initial infusion, at 7 weeks after the initial infusion, and at 8 weeks after the initial infusion. In some examples, the first additional IV infusion is administered at 3 days after the initial IV infusion, at 6 days after the initial IV infusion, at 9 days after the initial IV infusion, at 12 days after the initial infusion, and at 15 days after the initial infusion, and the second additional IV infusion is administered at 3 weeks after the initial IV infusion, at 4 weeks after the initial IV infusion, at 5 weeks after the initial IV infusion, at 6 weeks after the initial infusion, at 7 weeks after the initial infusion, and at 8 weeks after the initial infusion.

[0011] In some examples, the first additional IV infusion and the second additional IV infusion are administered at different dosages. In some examples, the first additional IV infusion and the second additional IV infusion are administered at different dosages, where the second additional IV infusion dosage is higher than the first additional

IV infusion. In some examples, the first additional IV infusion and the second additional IV infusion are administered at different dosages, where the second additional IV infusion dosage is higher than the first additional IV infusion, and where both the first and the second additional IV infusion dosages are higher than the initial dosage. In some examples, at least one of the first and second additional IV infusions is administered at a dosage of 3mg/kg. In some examples, the first additional IV infusion is administered at a dosage of 3 mg/kg, and the second additional IV infusion is administered at a dosage of 6 mg/kg. In some examples, the first additional IV infusion is administered at least three days after the initial IV infusion. In some examples, the first additional IV infusion is administered at a time selected from the group consisting of at 3 days after the initial IV infusion, at 6 days after the initial IV infusion, at 9 days after the initial IV infusion, at 12 days after the initial infusion, and at 15 days after the initial infusion. In some examples, the first additional IV infusion is administered at 3 days after the initial IV infusion, at 6 days after the initial IV infusion, at 9 days after the initial IV infusion, at 12 days after the initial infusion, and at 15 days after the initial infusion. In some examples, the second additional IV infusion is administered at a time selected from the group consisting of at 3 weeks after the initial IV infusion, at 4 weeks after the initial IV infusion, at 5 weeks after the initial IV infusion, at 6 weeks after the initial infusion, at 7 weeks after the initial infusion, and at 8 weeks after the initial infusion. In some examples, the second additional IV infusion is administered at 3 weeks after the initial IV infusion, at 4 weeks after the initial IV infusion, at 5 weeks after the initial IV infusion, at 6 weeks after the initial infusion, at 7 weeks after the initial infusion, and at 8 weeks after the initial infusion. In some examples, the first additional IV infusion is administered at 3 days after the initial IV infusion, at 6 days after the initial IV infusion, at 9 days after the initial IV infusion, at 12 days after the initial infusion, and at 15 days after the initial infusion, and the second additional IV infusion is administered at 3 weeks after the initial IV infusion, at 4 weeks after the initial IV infusion, at 5 weeks after the initial IV infusion, at 6 weeks after the initial infusion, at 7 weeks after the initial infusion, and at 8 weeks after the initial infusion.

[0012] In some examples, the first additional IV infusion includes at least a first series of twice weekly IV infusions and the second additional IV infusion includes at least a second series of twice weekly IV infusions. In some examples, the first series of twice weekly IV infusions and the second series of twice weekly IV infusions are administered at

a dose higher than the initial dose of 1 mg/kg. In some examples, the first series of twice weekly IV infusions is administered at a dose of 3 mg/kg, and the second series of twice weekly IV infusions is administered at a dose of 6 mg/kg. In some examples, the first series of additional IV infusion is administered at least three days after the initial IV infusion. In some examples, the first series of additional IV infusions is administered at a time selected from the group consisting of at 3 days after the initial IV infusion, at 6 days after the initial IV infusion, at 9 days after the initial IV infusion, at 12 days after the initial infusion, and at 15 days after the initial infusion. In some examples, the first series of additional IV infusions is administered at 3 days after the initial IV infusion, at 6 days after the initial IV infusion, at 9 days after the initial IV infusion, at 12 days after the initial infusion, and at 15 days after the initial infusion. In some examples, the second series of additional IV infusions is administered at a time selected from the group consisting of at 3 weeks after the initial IV infusion, at 4 weeks after the initial IV infusion, at 5 weeks after the initial IV infusion, at 6 weeks after the initial infusion, at 7 weeks after the initial infusion, and at 8 weeks after the initial infusion. In some examples, the second series of additional IV infusions is administered at 3 weeks after the initial IV infusion, at 4 weeks after the initial IV infusion, at 5 weeks after the initial IV infusion, at 6 weeks after the initial infusion, at 7 weeks after the initial infusion, and at 8 weeks after the initial infusion. In some examples, the first series of additional IV infusions is administered at 3 days after the initial IV infusion, at 6 days after the initial IV infusion, at 9 days after the initial IV infusion, at 12 days after the initial infusion, and at 15 days after the initial infusion, and the second series of additional IV infusions is administered at 3 weeks after the initial IV infusion, at 4 weeks after the initial IV infusion, at 5 weeks after the initial IV infusion, at 6 weeks after the initial infusion, at 7 weeks after the initial infusion, and at 8 weeks after the initial infusion.

[0013] In some examples, infusions are performed every 3 days after the initial dose for up to 15 days after the initial dose. In some examples, infusions are performed every 3 days after the initial dose for up to 15 days after the initial dose, followed by infusions twice per week starting at least 15 days after the initial dose. In some examples, the infusion dosage is increased to 3 mg/kg at any point after the initial dose. In some examples, after a minimum of two infusions at 3 mg/kg, the dose of NI-0501 is increased to 6 mg/kg for up to four infusions.

[0014] In the compositions and methods provided herein, NI-0501 is administered

to a subject in need thereof for treating, preventing and/or delaying the onset or progression of, or alleviating a symptom associated with HLH. In some examples, NI-0501 is administered to a subject in need thereof by IV infusion over a period of one hour at an initial dose of 1 mg/kg. In some examples, infusions are performed every 3 days after the initial dose for up to 15 days after the initial dose. In some examples, infusions are performed every 3 days after the initial dose for up to 15 days after the initial dose, followed by infusions twice per week starting at least 15 days after the initial dose. In some examples, the infusion dosage is increased to 3 mg/kg at any point after the initial dose. In some examples, after a minimum of two infusions at 3 mg/kg, the dose of NI-0501 is increased to 6 mg/kg for up to four infusions.

[0015] In the compositions and methods provided herein, NI-0501 is administered to a subject in need thereof for treating, preventing and/or delaying the onset or progression of, or alleviating a symptom associated with HLH. In some examples, NI-0501 is administered to a subject in need thereof by IV infusion for a dosage of greater than 6 mg/kg. In some examples, NI-0501 is administered to a subject in need thereof by IV infusion, after an initial dosage, for a second dosage of greater than 6 mg/kg. In some examples, the second dosage is at least 10 mg/kg. In some examples, the second dosage is 10 mg/kg. In some examples, the second dosage is 10 mg/kg, repeated daily. In some examples, the second dosage is 10 mg/kg, repeated daily for 1 week. In some examples, the second dosage is 10 mg/kg, repeated daily for 2 weeks. In some examples, the second dosage is 10 mg/kg, repeated daily for more than 2 weeks.

[0016] In some examples, NI-0501 is administered to a subject in need thereof for treating, preventing and/or delaying the onset or progression of, or alleviating a symptom associated with secondary HLH. In some examples, NI-0501 is administered to a subject in need thereof for treating, preventing and/or delaying the onset or progression of, or alleviating a symptom associated with secondary HLH on a background of sJIA. In some examples, NI-0501 is administered to a subject in need thereof as an initial dose of 6 mg/kg. In some examples, the NI-0501 treatment is continued with a subsequent NI-0501 dose. In some examples, the NI-0501 treatment is continued with a subsequent NI-0501 dose of 3 mg/kg every 3 days for at least 4 weeks (i.e., up to SD27).

[0017] In some examples, NI-0501 treatment is reduced, stopped, or otherwise shortened upon achievement of a desired clinical outcome. In some examples, NI-0501 treatment is shortened upon evidence of complete clinical response, i.e., MAS remission.

[0018] In some examples, after 4 weeks, NI-0501 treatment is continued for up to an additional 4 weeks (i.e., up to SD56) as maintenance as needed until MAS remission is achieved. In some examples, after 4 weeks, NI-0501 treatment is continued for up to an additional 4 weeks (i.e., up to SD56) as maintenance as needed until MAS remission is achieved, with the possibility of decreasing the dose to 1 mg/kg and elongating the interval between infusion to weekly administration.

[0019] In the compositions and methods provided herein, NI-0501 is administered to a subject in need thereof for treating, preventing and/or delaying the onset or progression of, or alleviating a symptom associated with HLH, where the subject has been administered a background of dexamethasone. In some examples, the subject is a treatment-naïve patient (i.e., has not previously been treated for HLH), and the dexamethasone is administered at a dose of at least 10 mg/m². In some examples, the subject is receiving NI-0501 as a second line HLH treatment, and the dexamethasone is administered at a dose of in the range of 10 mg/m² to 5 mg/m². In some examples, the subject is receiving NI-0501 as a second line HLH treatment, and the dexamethasone is administered at a dose of at least 5 mg/m². In some examples, the subject is receiving NI-0501 as a second line HLH treatment, and the dexamethasone is administered at a dose of less than 5 mg/m².

[0020] In some examples, NI-0501 is administered before and/or during and/or after treatment in combination with one or more additional agents such as, by way of non-limiting example, a therapeutic agent, an anti-inflammatory agent, and/or an immunosuppressive agent. In some examples, the second agent is an agent known to be used in the treatment of HLH. In some examples, the additional agent includes at least etoposide. In some examples, NI-0501 and the additional agent are formulated into a single therapeutic composition, and NI-0501 and additional agent are administered simultaneously. Alternatively, NI-0501 and additional agent are separate from each other, *e.g.*, each is formulated into a separate therapeutic composition, and NI-0501 and the additional agent are administered simultaneously, or NI-0501 and the additional agent are administered at different times during a treatment regimen. For example, NI-0501 is administered prior to the administration of the additional agent, NI-0501 is administered subsequent to the administration of the additional agent, or NI-0501 and the additional agent are administered in an alternating fashion. As described herein, NI-0501 and additional agent are administered in single doses or in multiple doses.

[0021] In some examples, NI-0501 and the additional agent(s) are administered

simultaneously. For example, NI-0501 and the additional agent(s) can be formulated in a single composition or administered as two or more separate compositions. In some examples, NI-0501 and the additional agent(s) are administered sequentially, or NI-0501 and the additional agent are administered at different times during a treatment regimen.

[0022] In some examples, the additional agent is an immunosuppressive agent. In some examples, the immunosuppressive agent is Cyclosporin A (CsA). In some examples, the subject has been receiving CsA prior to administration of NI-0501. In some examples, the additional agent includes at least etoposide. In some examples, the subject has been receiving etoposide prior to administration of NI-0501.

[0023] In some examples, the additional agent is intrathecal methotrexate and/or glucocorticoids. In some examples, the subject has been receiving intrathecal methotrexate and/or glucocorticoids prior to administration of NI-0501.

[0024] In some examples, the additional agent is IV immunoglobulins (IVIG). In some examples, the IVIG is administered as replacement treatment in a subject with a documented immunoglobulin deficiency. In some examples where the subject has a documented immunoglobulin deficiency, IVIG is administered given at a dose of 0.5 g/kg, every 4 weeks or more frequently in order to maintain adequate IgG levels.

[0025] In some examples, the one or more additional agents is analgesic treatment, transfusion of blood products, electrolyte and glucose infusions, antibiotics, anti-fungal and anti-viral treatment and/or general supportive care.

[0026] The disclosure also provides compositions and methods that are useful in identifying or otherwise refining a patient population suffering from a disorder, where the patient has an elevated level of CXCL9, alone or in combination with one or more additional interferon γ (IFN γ) related biomarkers. In particular, the disclosure provides compositions and methods for detecting CXCL9 levels as a biomarker for IFN γ production in patients suffering from or suspected of suffering from hemophagocytic lymphohistiocytosis (HLH). In particular, the disclosure provides compositions and methods for detecting CXCL9 levels as a biomarker for IFN γ production in patients suffering from or suspected of suffering from secondary hemophagocytic lymphohistiocytosis (HLH). In some examples, the compositions and methods are used to detect CXCL9 levels as a biomarker for IFN γ production in patients suffering from or suspected of suffering from macrophage activation syndrome (MAS). In some examples, the compositions and methods are used to detect CXCL9 levels as a

biomarker for IFN γ production in patients suffering from or suspected of suffering from MAS in the context of an autoimmune disease or inflammatory disorder. In some examples, the compositions and methods are used to detect CXCL9 levels as a biomarker for IFN γ production in patients suffering from or suspected of suffering from MAS in the context of a systemic autoimmune disease or inflammatory disorder. In some examples, the compositions and methods are used to detect CXCL9 levels as a biomarker for IFN γ production in patients suffering from or suspected of suffering from MAS in the context of systemic Juvenile Idiopathic Arthritis (sJIA). In some examples, the compositions and methods are used to detect CXCL9 levels as a biomarker for IFN γ production in patients suffering from or suspected of suffering from MAS in the context of Systemic Lupus Erythematosus (SLE).

[0027] Patients identified as having elevated levels of CXCL9 are identified as suitable candidates for treatment with an agent (*e.g.*, antibodies or other polypeptide-based therapeutics, peptide-based therapeutics, small molecule inhibitors, nucleic acid-based therapeutics and derivatives thereof) that interferes with or otherwise antagonizes one or more biological activities of IFN γ such as, for example, IFN γ signaling, and neutralizes at least one biological activity of IFN γ .

[0028] In some patients suffering from or suspected of suffering from a disorder, fluids and other biological samples contain elevated levels of CXCL9, alone or in combination with other IFN γ -related biomarkers such as, for example, CXCL10 and/or CXCL11.

[0029] CXCL9 and these other biomarkers are indicators of *in vivo* IFN γ production. Thus, use of an anti-IFN γ antagonist that interferes with, inhibits, reduces or otherwise antagonizes IFN γ signaling, *e.g.*, a neutralizing anti-IFN γ antibody or other polypeptide-based therapeutic, a peptide-based therapeutic, a small molecule inhibitor, a nucleic acid-based therapeutic and derivatives thereof, blocks or otherwise inhibits IFN γ activity. Thus, the compositions and methods are useful in treating, delaying the progression of or otherwise ameliorating a symptom of a disorder that is dependent on, driven by, associated with, or otherwise impacted by aberrant, *e.g.*, elevated, IFN γ expression and/or activity, aberrant pro-inflammatory cytokine production and/or combinations thereof, by administering an anti-IFN γ antagonist, *e.g.*, a neutralizing anti-IFN γ antibody or other polypeptide-based therapeutic, a peptide-based therapeutic, a small molecule inhibitor, a

nucleic acid-based therapeutic and derivatives thereof, to patients exhibiting an elevated level of expression CXCL9 and/or other biomarkers. Patients that are likely suitable candidates for treatment with the anti-IFN γ antagonist, *e.g.*, neutralizing anti-IFN γ antibody such as those described herein, are identified by detecting the level of CXCL9, alone or in combination with one or more IFN γ -related ligands or other biomarkers. In some examples, patients that do not have elevated levels of CXCL9, alone or in combination with other IFN γ -related biomarkers may still be treated with an anti-IFN γ antagonist, including any of the neutralizing anti-IFN γ antibodies described herein or other polypeptide-based therapeutic, a peptide-based therapeutic, a small molecule inhibitor, a nucleic acid-based therapeutic and derivatives thereof.

[0030] Patients with elevated levels of CXCL9, alone or in combination with one or more additional IFN γ -related biomarkers are identified as suitable candidates for therapy with one or more anti-IFN γ antagonists, *e.g.*, a neutralizing anti-IFN γ antibody described herein. As used herein, the phrase “elevated level of expression” refers to a level of expression that is greater than a baseline level of expression of CXCL9, alone or in combination with one or more additional biomarkers, in a sample from a patient that is not suffering from or suspected of suffering from primary or secondary HLH or HLH-related disorder, or from another control sample. In some examples, the elevated level of expression of CXCL9 and/or other biomarker is a significant level of elevation.

[0031] The detected level of CXCL9, alone or in combination with one or more other IFN γ -related biomarkers, is useful to refine or otherwise stratify a patient population. In some examples, the detected level is used to determine the dosage of anti-IFN γ antagonist that should be administered to a given patient. In some examples, the detected level is used to categorize or otherwise stratify a patient population. For example, patients can be classified as having “severe” or high grade MAS, or conversely, not severe or low grade MAS, based on the detected level of CXCL9.

[0032] The sample is, for example, blood or a blood component, *e.g.*, serum, plasma. In some examples, the sample is another bodily fluid such as, by way of non-limiting example, urine, synovial fluid, bronchial alveolar fluid, cerebrospinal fluid, broncho-alveolar lavage (BAL), and/or saliva. In some examples, the biological sample is CSF. In some examples, the biological sample is CSF from an HLH patient.

[0033] In addition to detecting the level of IFN γ and/or other IFN γ -related biomarkers, suitable patients for treatment with an anti-IFN γ antagonist can also be

identified by evaluating any of a number of additional biological and clinical parameters that will improve the sensitivity and specificity of the biomarker for identifying or otherwise refining the patient population. Alternatively, these additional biological and clinical parameters can be used alone as a means for identifying patients that are suitable candidates for treatment with an anti-IFN γ antagonist or other suitable therapy. These biological and clinical parameters include, by way of non-limiting example, any of the following: ferritin levels, neutrophil count, platelet count, alanine aminotransferase levels, and/or lactate dehydrogenase levels.

[0034] Disorders that are useful with the compositions and methods of the disclosure include any disorder where aberrant, *e.g.*, elevated, IFN γ expression and/or activity, particularly HLH, including secondary HLH, MAS, and/or sJIA.

[0035] By way of non-limiting examples, the methods and compositions provided herein are suitable for diagnosing and/or treating disorders such as primary and/or secondary HLH disorders. Suitable autoimmune and/or inflammatory disorders include, by way of non-limiting example, primary and/or secondary HLH disorders associated with aberrant IFN γ activity and/or expression.

[0036] Once patients are identified as having an elevated level of CXCL9, alone or in combination with one or more IFN γ -related biomarkers, they are then treated with an anti-IFN γ antagonist. For example, the anti-IFN γ antagonist is a neutralizing anti-IFN γ antibody or an immunologically active (*e.g.*, antigen binding) fragment thereof. Suitable neutralizing anti-IFN γ antibodies include any of the anti-IFN γ antibodies described herein.

[0037] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises a variable heavy chain complementarity determining region 1 (VH CDR1) comprising an amino acid sequence at least 90%, 92%, 95%, 96%, 97% 98%, 99% or more identical to the amino acid sequence of SYAMS (SEQ ID NO: 1); a variable heavy chain complementarity determining region 2 (VH CDR2) comprising an amino acid sequence at least 90%, 92%, 95%, 96%, 97% 98%, 99% or more identical to the amino acid sequence of AISGSGGSTYYADSVKG (SEQ ID NO: 2); and a variable heavy chain complementarity determining region 3 (VH CDR3) comprising an amino acid sequence at least 90%, 92%, 95%, 96%, 97% 98%, 99% or more identical to the amino acid sequence of DGSSGWYVPHWFDP (SEQ ID NO: 3); a variable light chain complementarity determining region 1 (VL CDR1) comprising an amino acid sequence at least 90%, 92%, 95%, 96%, 97% 98%, 99% or more identical to the amino acid sequence of

TRSSGSIASNYVQ (SEQ ID NO: 4); a variable light chain complementarity determining region 2 (VL CDR2) comprising an amino acid sequence at least 90%, 92%, 95%, 96%, 97% 98%, 99% or more identical to the amino acid sequence of EDNQRPS (SEQ ID NO: 5); and a variable light chain complementarity determining region 3 (VL CDR3) comprising an amino acid sequence at least 90%, 92%, 95%, 96%, 97% 98%, 99% or more identical to the amino acid sequence of QSYDGSNRWM (SEQ ID NO: 6).

[0038] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises a VH CDR1 comprising the amino acid sequence of SYAMS (SEQ ID NO: 1); a VH CDR2 region comprising the amino acid sequence of AISGSGGSTYYADSVKG (SEQ ID NO: 2); and a VH CDR3 region comprising the amino acid sequence of DGSSGWYVPHWFDP (SEQ ID NO: 3); a variable light chain complementarity determining region 1 (VL CDR1) region comprising the amino acid sequence of TRSSGSIASNYVQ (SEQ ID NO: 4); a VL CDR2 region comprising the amino acid sequence of EDNQRPS (SEQ ID NO: 5); and a VL CDR3 region comprising the amino acid sequence of QSYDGSNRWM (SEQ ID NO: 6).

[0039] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises a heavy chain that comprises a combination of a VH CDR1 sequence, a VH CDR2 sequence, and a VH CDR3 sequence, wherein the combination is a combination of the three heavy chain CDR sequences (VH CDR1, VH CDR2, VH CDR3) shown in a single row in Table 1A.

[0040] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises a light chain that comprises a combination of a VL CDR1 sequence, a VL CDR2 sequence, and a VL CDR3 sequence, wherein the combination is a combination of the three light chain CDR sequences (VL CDR1, VL CDR2, VL CDR3) shown in a single row in Table 1B.

[0041] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises a heavy chain that comprises a combination of a VH CDR1 sequence, a VH CDR2 sequence, and a VH CDR3 sequence, wherein the combination is a combination of the three heavy chain CDR sequences (VH CDR1, VH CDR2, VH CDR3) shown in a single row in Table 1A, and a light chain that comprises a combination of a VL CDR1 sequence, a VL CDR2 sequence, and a VL CDR3 sequence, wherein the combination is a combination of the three light chain CDR sequences (VL CDR1, VL CDR2, VL CDR3) shown in a single row in Table 1B.

[0042] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises an amino acid sequence at least 90%, 92%, 95%, 96%, 97%, 98%, 99% or more identical to the heavy chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 47.

[0043] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises an amino acid sequence at least 90%, 92%, 95%, 96%, 97%, 98%, 99% or more identical to the light chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 48.

[0044] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises an amino acid sequence at least 90%, 92%, 95%, 96%, 97%, 98%, 99% or more identical to the heavy chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 47, and an amino acid sequence at least 90%, 92%, 95%, 96%, 97%, 98%, 99% or more identical to the light chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 48.

[0045] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises the heavy chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 47.

[0046] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises the light chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 48.

[0047] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises the heavy chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 47, and the light chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 48.

[0048] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises an amino acid sequence at least 90%, 92%, 95%, 96%, 97%, 98%, 99% or more identical to the heavy chain amino acid sequence to the amino acid sequence of SEQ ID NO: 44.

[0049] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises an amino acid sequence at least 90%, 92%, 95%, 96%, 97%, 98%, 99% or more identical to the light chain amino acid sequence to the amino acid sequence of SEQ ID NO: 46.

[0050] In some examples, the anti-IFN γ antibody or immunologically active

fragment thereof comprises an amino acid sequence at least 90%, 92%, 95%, 96%, 97%, 98%, 99% or more identical to the heavy chain amino acid sequence to the amino acid sequence of SEQ ID NO: 44, and an amino acid sequence at least 90%, 92%, 95%, 96%, 97%, 98%, 99% or more identical to the light chain amino acid sequence to the amino acid sequence of SEQ ID NO: 46.

[0051] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises the heavy chain amino acid sequence to the amino acid sequence of SEQ ID NO: 44.

[0052] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises the light chain amino acid sequence to the amino acid sequence of SEQ ID NO: 46.

[0053] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises the heavy chain amino acid sequence to the amino acid sequence of SEQ ID NO: 44, and the light chain amino acid sequence to the amino acid sequence of SEQ ID NO: 46.

[0054] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises an amino acid sequence at least 90%, 92%, 95%, 96%, 97%, 98%, 99% or more identical to a heavy chain variable amino acid sequence selected from the group consisting of SEQ ID NOs: 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98, and 102.

[0055] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises an amino acid sequence at least 90%, 92%, 95%, 96%, 97%, 98%, 99% or more identical to a light chain variable amino acid sequence selected from the group consisting of SEQ ID NOs: 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, and 104.

[0056] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises an amino acid sequence at least 90%, 92%, 95%, 96%, 97%, 98%, 99% or more identical to a heavy chain variable amino acid sequence selected from the group consisting of SEQ ID NOs: 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98, and 102, and an amino acid sequence at least 90%, 92%, 95%, 96%, 97%, 98%, 99% or more identical to a light chain variable amino acid sequence selected from the group consisting of SEQ ID NOs: 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, and 104.

[0057] In some examples, the anti-IFN γ antibody or immunologically active

fragment thereof comprises a heavy chain variable amino acid sequence selected from the group consisting of SEQ ID NOs: 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98, and 102.

[0058] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises a light chain variable amino acid sequence selected from the group consisting of SEQ ID NOs: 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, and 104.

[0059] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof comprises a heavy chain variable amino acid sequence selected from the group consisting of SEQ ID NOs: 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98, and 102, and a light chain variable amino acid sequence selected from the group consisting of SEQ ID NOs: 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, and 104.

[0060] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof is administered in a therapeutically effective amount. A therapeutically effective amount of an antibody of the disclosure relates generally to the amount needed to achieve a therapeutic objective. This therapeutic objective may be a binding interaction between the antibody and its target antigen that, in certain cases, interferes with the functioning of the target. Common ranges for therapeutically effective dosing of an antibody or antibody fragment of the disclosure may be, by way of nonlimiting example, from about 0.1 mg/kg body weight to about 50 mg/kg body weight. Common dosing frequencies may range, for example, from twice daily to once a week.

[0061] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof is administered at an initial dose, i.e., load dose, in the range from about 0.5 mg/kg to about 2 mg/kg, for example, in a range from about 0.5 mg/kg to about 1.5 mg/kg, and/or from about 0.5 mg/kg to about 1.0 mg/kg. In some examples, the anti-IFN γ antibody or immunologically active fragment thereof is administered at an initial dose of about 1.0 mg/kg.

[0062] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof is administered as an initial load dose followed by one or more maintenance doses. In some examples, the one or more maintenance dose(s) is a dosage that is substantially similar to the initial load dose. In some examples, the one or more maintenance dose(s) is a dosage that is less than the initial load dose. In some examples, the one or more maintenance dose(s) is a dosage that is greater than the initial load dose.

[0063] In some examples, the one or more maintenance dose(s) comprises at

least two or more dosages, wherein each maintenance dosage is the same dosage. In some examples, the two or more maintenance dosages are substantially similar to the initial load dose. In some examples, the two or more maintenance dosages are greater than the initial load dose. In some examples, the two or more maintenance dosages are less than the initial load dose.

[0064] In some examples, the one or more maintenance dose(s) comprises at least two or more dosages, wherein each maintenance dosage is not the same dosage. In some examples, the two or more maintenance dosages are administered in an increasing dosage amount. In some examples, the two or more maintenance dosages are administered in a decreasing dosage amount.

[0065] In some examples, the one or more maintenance dose(s) comprises at least two or more dosages, wherein each maintenance dosage is administered at a periodic time interval. In some examples, two or more dosages are administered at increasing time intervals. In some examples, two or more dosages are administered at decreasing time intervals.

[0066] In some examples, the anti-IFN γ antibody or immunologically active fragment thereof is administered at an initial load dose in the range from about 0.5 mg/kg to about 2 mg/kg, for example, in a range from about 0.5 mg/kg to about 1.5 mg/kg, and/or from about 0.5 mg/kg to about 1.0 mg/kg, followed by at least one, e.g., two or more, three or more, four or more, or five or more maintenance doses. In some examples, the anti-IFN γ antibody or immunologically active fragment thereof is administered at an initial load dose of about 1.0 mg/kg, followed by at least one, e.g., two or more, three or more, four or more, or five or more maintenance doses.

[0067] Pharmaceutical compositions according to the disclosure can include an anti-IFN γ antibody of the disclosure and a carrier. These pharmaceutical compositions can be included in kits, such as, for example, diagnostic kits.

[0068] The disclosure also provides kits for practicing any of the methods provided herein. For example, in some examples, the kits include a detection reagent specific for CXCL9, alone or in combination with one or more IFN γ -related biomarkers and a means for detecting the detection reagent.

Brief Description of the Drawings

[0069] Figure 1 is a graph depicting correlations between predose serum CXCL9

What is claimed is:

1. Use of an anti-interferon gamma (IFN γ) antagonist in the manufacture of a medicament for alleviating a symptom of a disorder, wherein a level of CXCL9 is detected, alone or in conjunction with one or more other biomarkers in a biological sample from a subject, the detected level of CXCL9 is compared to a control level of expression, and when the detected level is elevated, the medicament is to be administered in an amount sufficient to alleviate the symptom of the disorder to the subject.
2. The use of claim 1, wherein the one or more other biomarkers is selected from the group consisting of total IFN γ level, CXCL10, CXCL11, and combinations thereof.
3. The use of claim 1, wherein the biological sample is or is derived from blood.
4. The use of claim 1, wherein the biological sample is serum.
5. The use of claim 1, wherein the anti-IFN γ antagonist is an anti-IFN γ antibody or immunologically active fragment thereof.
6. The use of claim 5, wherein the anti-IFN γ antibody or immunologically active fragment thereof comprises a variable heavy chain complementarity determining region 1 (VH CDR1) comprising the amino acid sequence of SYAMS (SEQ ID NO: 1); a variable heavy chain complementarity determining region 2 (VH CDR2) comprising the amino acid sequence of AISGSGGSTYYADSVKG (SEQ ID NO: 2); a variable heavy chain complementarity determining region 3 (VH CDR3) comprising the amino acid sequence of DGSSGWYVPHWFDP (SEQ ID NO: 3); a variable light chain complementarity determining region 1 (VL CDR1) region comprising the amino acid sequence of TRSSGSIASNYVQ (SEQ ID NO: 4); a variable heavy chain complementarity determining region 2 (VL CDR2) comprising the amino acid sequence of EDNQRPS (SEQ ID NO: 5); and a variable heavy chain complementarity determining region 3 (VL CDR3) comprising the amino acid sequence of QSYDGSNRWM (SEQ ID NO: 6).
7. The use of claim 5, wherein the anti-IFN γ antibody or immunologically active

fragment thereof comprises the heavy chain variable amino acid sequence of SEQ ID NO: 47 and the light chain variable amino acid sequence of SEQ ID NO: 48.

8. The use of claim 5, wherein the anti-IFN γ antibody or immunologically active fragment thereof comprises the heavy chain amino acid sequence of SEQ ID NO: 44 and the light chain amino acid sequence of SEQ ID NO: 46.

9. The use of claim 1, wherein the subject is human.

10. The use of claim 1, wherein the disorder is an autoimmune or inflammatory disorder.

11. The use of claim 1, wherein the disorder is primary or secondary hemophagocytic lymphohistiocytosis (HLH).

12. The use of claim 1, wherein the disorder is macrophage activation syndrome (MAS).

13. The use of claim 1, wherein the disorder is MAS in the context of systemic Juvenile Idiopathic Arthritis (sJIA).

14. The use of claim 1, wherein the subject has received an allogeneic hematopoietic stem cell transplant.

15. The use of claim 14, wherein the disorder is graft failure.

16. The use of claim 1, wherein the disorder is paraneoplastic cerebellar degeneration, hemorrhagic fever, sarcoidosis, adult onset Still's disease, transplant failure, transplant rejection, and/or an inflammatory disorder associated with transplant rejection.

17. The use of claim 16, wherein the transplant rejection is a solid organ transplant disorder, a bone marrow rejection, or an acute graft rejection.

18. The use of claim 1, wherein the disorder is a side effect of CAR-T cell therapy.

19. The use of claim 1, wherein the symptom of the disorder is an increased level of ferritin, neutrophil, platelet counts and/or alanine aminotransferase (ALT) in comparison to a control level.
20. The use of claim 1, wherein CXCL9 is detected by contacting the sample with an anti-CXCL9 antibody and detecting binding between CXCL9 and the anti-CXCL9 antibody.
21. Use of an anti-interferon gamma (IFN γ) antagonist in the manufacture of a medicament for preventing graft failure in a patient who has received or will receive an allogeneic hematopoietic stem cell transplant.
22. The use of claim 21, wherein the anti-IFN γ antagonist is an anti-IFN γ antibody or immunologically active fragment thereof.
23. The use of claim 21, wherein the anti-IFN γ antibody or immunologically active fragment thereof comprises a variable heavy chain complementarity determining region 1 (VH CDR1) comprising the amino acid sequence of SYAMS (SEQ ID NO: 1); a variable heavy chain complementarity determining region 2 (VH CDR2) comprising the amino acid sequence of AISGSGGSTYYADSVKG (SEQ ID NO: 2); a variable heavy chain complementarity determining region 3 (VH CDR3) comprising the amino acid sequence of DGSSGWYVPHWFDP (SEQ ID NO: 3); a variable light chain complementarity determining region 1 (VL CDR1) region comprising the amino acid sequence of TRSSGSIASNYVQ (SEQ ID NO: 4); a variable heavy chain complementarity determining region 2 (VL CDR2) comprising the amino acid sequence of EDNQRPS (SEQ ID NO: 5); and a variable heavy chain complementarity determining region 3 (VL CDR3) comprising the amino acid sequence of QSYDGSNRWM (SEQ ID NO: 6).
24. The use of claim 21, wherein the anti-IFN γ antibody or immunologically active fragment thereof comprises the heavy chain variable amino acid sequence of SEQ ID NO: 47 and the light chain variable amino acid sequence of SEQ ID NO: 48.

25. The use of claim 21, wherein the anti-IFN γ antibody or immunologically active fragment thereof comprises the heavy chain amino acid sequence of SEQ ID NO: 44 and the light chain amino acid sequence of SEQ ID NO: 46.